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# General Address on Chemio-Therapy

BY

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# GENERAL ADDRESS ON

# CHEMIO-THERAPY

By Seine Exzellenz Wirklicher Geheimer Rat
Professor Dr. PAUL EHRLICH

It must be a great pleasure and a special honour for all of us to meet here personally on British soil for a scientific purpose, in order to take part in the great work which will be of benefit to the whole world. Are we not here in a country that has produced two men who must be considered among the greatest men of all times, Jenner and Lord Lister? Like a star in the darkness of his age, Jenner's great achievement, which broke the power of such an awful public plague as small-pox, still shines with peerless splendour. And on the occasion of the last Congress which was held here we gathered with wondering admiration round Lord Lister, who through his introduction of antiseptics brought about a revolution in surgery which stands alone in the history of medicine. Here in England the first example of a modern Institute for Tropical Diseases, which is a model for all other institutes of this kind, was created under the direction of Sir Patrick Manson. Through Ross's excellent work, Laveran's discovery of the causes of malaria was so far advanced that entirely new lines were opened up for the hygienic struggle against tropical and subtropical diseases.

The proof by Castellani that a trypanosome is the cause of sleeping sickness, the classical work by Bruce on illnesses caused through trypanosomes, the specific cause of kala-azar (Dum-dum sickness) as proved by Leishman, are all well known to us. The therapeutic influence of atoxyl in the cases of trypanosome diseases was first established in the Liverpool Tropical Institute by Thomas and Breinl, and quite recently Plimmer has brought forward the use of tartar emetic as an effective weapon against protozoal diseases.

The life-work of Almroth Wright is also known to all of us, i. e. his work on opsonins and on the prophylactic treatment of typhoid fever, which has been carried out in a practical and most excellent manner. Even these few names, to which I might add many others, show what a high and leading position England has taken and still holds in the fight against infectious diseases. To prevent the spread of and to heal infectious diseases was at all times the highest aim of medical aspirations; however, a systematic pursuit of this purpose has only been possible in recent times, as through the labours of all civilized nations we have got an

insight into the nature of infections, the cause of diseases, and the means by which they are transmitted. Through these methods it has been possible to infect animals artificially and so obtain material on which to test the drugs in a systematic and rational manner. From the very first beginnings of therapeutics, chemio-therapy has indeed been in existence, as all the remedies which we employ are chemicals ; on the other hand, experimental chemio-therapy could only develop in modern times in a fruitful manner as a result of all this pioneer work. But here also it has been proved that the four most important factors are : *patience, skill, luck,* and, last but not least, *money.*

Now, gentlemen, I may perhaps take the liberty of giving you an insight into the workshop of the chemio-therapeutic work. The whole area is governed by a simple, I might even say natural, principle. If the law is true in chemistry that ' Corpora non agunt nisi liquida ', then for chemio-therapy the principle is true that ' Corpora non agunt nisi fixata '. When applied to the special case in point this means that parasites are only killed by those materials to which they have a certain relationship, by means of which they are fixed by them. I call such substances 'parasitotropic '. But I should like immediately to add that there are evident exceptions to this law. So, for instance, we are acquainted with a small series of cases in which the apparent therapeutic results are obtained although the allied substances in question do not possess parasite-destroying qualities. That is the case in the infiltration of the subcutaneous tissues which is caused by a kind of yeast (sporotrichosis). Here Block proved that the clinically highly therapeutic iodide of potassium first of all dissolves the cells of the infiltration, whilst the parasites, as such, are not in the first instance attacked.

But, in any case, it is safest and best for the development of chemio-therapy not to build on the basis of exceptional work, but it is better to start with such substances which produce the destruction of the parasites by fixation.

Now it has been assumed in different quarters that some of the more modern remedies are incorrectly regarded as parasiticides, but in reality they are not such. Thus, for example, salvarsan or mercury salts are not intended to act directly on the parasites, but indirectly, owing to the fact that they excite the organism to the formation of specific anti-substances. This view is based mainly upon the fact that if one mixes the substances in question, such as, for instance, neosalvarsan, with certain pathogenic agents, e.g. spirochætes, in test-tubes one cannot perceive any reduction in their mobility after observing them for hours together. From this fact, which was first discovered by Professor Hata, the conclusion has been drawn that salvarsan or neosalvarsan, as such, did not in any way directly influence the spirochætes. Now it can very easily be shown that this conclusion is quite incorrect. If, for instance, following Castelli, one suspends the spirochætes of relapsing fever in indifferent mixtures of serum which do not injure their vitality, and if

one fills two small tubes therewith and adds to one of the tubes a very small quantity of salvarsan or neosalvarsan, and if one then centrifugalizes and then draws off the liquid ; if one washes the remaining spirochætes again in a mixture of serum and again centrifugalizes it ; then one obtains in both tubes a deposit of spirochætes which on microscopic examination shows the same properties, i.e. equally good mobility of the spirochætes. If, however, the spirochætes obtained in this manner are injected into test mice, then one can very soon convince oneself that the spirilla treated with salvarsan do not give any infection to the animal, whilst the mice vaccinated with the contents of the control tube promptly show signs of infection. This proves that salvarsan or neosalvarsan, as the case may be, is absorbed by the spirochætes, and must have damaged them, and that this trace of salvarsan which is so exceedingly minute that it can scarcely be weighed, was sufficient to prevent the increase of the parasites in the animal body. Therefore, by this very simple and easily intelligible experiment, the direct effect of salvarsan and neosalvarsan on the spirochætes, and thereby the principle of fixation, is absolutely proved ; the objection of the indirect effect based upon anti-substances therefore falls to the ground.

It was necessary, however, to penetrate more deeply into the mechanism of this fixation of remedies, and it is only after long-continued efforts that success has been attained in obtaining a clear conception. In order to make practical progress it appeared to be necessary not to be satisfied with the primordial idea, but to see in what manner the drugs are fixed by the parasites or, as the case may be, by the cells. Only by taking a very roundabout way has it been possible to obtain clearness with respect to these complicated relations, and in this connexion it was especially the studies on trypanosomes, and especially the investigations of ' drug-fast ' strains of germs, which led to quite definite representations with regard to the process of fixation. There was no difficulty by continued treatment of the experimental mice with certain definite remedies, e.g. fuchsin, in finally obtaining a race of trypanosomes which had become immune against these remedies, i.e. ' drug-fast ', in the case mentioned above immune to fuchsin. There were especially three classes of different remedies which were very suited to this purpose :

1. The class of the arsenic compounds (in the following historical order : arsenious acid, arsenilic acid (atoxyl), arsenophenylglycin (salvarsan and neosalvarsan).

2. The class of the so-called azo-dyes (the trypan red manufactured by Weinberg, with which Shiga and I made experiments, and the trypan blue of Mesnil).

3. Certain basic triphenylmethan dyes (fuchsin, methyl violet, &c.).

When a race of trypanosomes has been rendered immune against fuchsin, then this race is immune against all the allies of fuchsin and methyl violet, &c., but is not immune against the two other classes.

Also a race immune against arsenic compounds is only immune against such, but not against the two other classes. We see, therefore, that the immunity is of a specific nature inasmuch as it is limited to a definite class of chemical substances.

It was just this specific character which indicated that it must be a question of purely chemical processes. Earlier studies relating to another subject, i.e. those relating to toxins and antitoxins, pointed to the nature of the said processes. In connexion with these it had been shown that the destructive toxins developed their injurious action on the cell by the fact that they are absorbed by certain specific component parts of the cell—side-chains—which I have characterized as ' receptors ', and that the anti-substances represent nothing else than the cell receptors produced in excess under the influence of the toxin and thrown off.

For many reasons I had hesitated about transferring these views relating to receptors to chemical bodies at all, and in this connexion it was especially the brilliant investigations by Langley relating to the effects of alkaloids which caused my doubts to disappear and made the existence of chemo-receptors seem probable to me.

From this point of view, the phenomena observed in connexion with the ' drug-fast ' strain of germs can be readily explained experimentally, owing to the fact that the chemo-receptors under the influence of drug-fastness suffer a reduction of their affinity for certain groupings connected with the remedy, which can only be regarded as purely chemical. This reduction in affinity explains in the simplest possible manner why continually increasing quantities of the arsenic compound become necessary for the destruction, e.g., of a race of arsenic-fast trypanosomes, for the smaller avidity can only be overcome by a corresponding surplus of the arsenic compound, if the quantity necessary for the destruction of the parasites is to be finally fixed.

We, therefore, come to the conclusion that in the parasites there are present *different specific chemo-receptors* ; for instance, the *arseno-receptor*, which fixes the trivalent group of arsenic as such, and the *acetico-receptor*, which fastens to itself the acetic acid group ; an *iodine-receptor* ; an *ortho-amidophenol-receptor*, which conditions the fixation of the salvarsan ; and many others in addition. A complete exhaustive knowledge of all the different chemo-receptors of a certain definite parasite is what I should like to characterize as the *therapeutic physiology of the parasite cell*, and this is a *sine qua non* of any successful chemio-therapeutic treatment. I should like to emphasize the fact that many observations indicate that certain chemo-receptors are due to several different kinds of parasites, not to a single one. The knowledge of these is of special practical importance, because remedies which are adjusted to these have a healing influence on a very large series of the most various pathogenic agents. *The larger the number of different chemo-receptors, therefore, which can be demonstrated the greater is the possibility of a successful chemio-therapy.*

Now if we seek for specific remedies, then the first condition is that they must possess a certain definite grouping, which is chemically allied to one of the chemo-receptors of the parasite. This is only a necessary prior condition of the toxic effect, but in general it is not a sufficient one in itself. Hundreds of substances may fix themselves on a parasite and only a few are capable of bringing about its destruction.

In the therapeutically suitable substance there must, therefore, in addition to the fixing group, which brings about the fixation of the *haptophoræ*, be another, which as such brings about the destruction, and which therefore is to be characterized as the ' poisoning ' or *toxophoric*. This representation exactly corresponds to the views which we have already long since obtained with respect to toxins, in which we distinguish the presence of a haptophoric group which conditions the cell fixation and also the formation of the antitoxins, and a toxophoric group which brings about the injurious action on the cell. In the case of the highly-complicated synthetic drugs the assumption will have to be made that the haptophoric group and the toxophoric group are not *directly* connected with one another, but as separate groups are linked with a chemical molecule in the character of side-chains. In this way we arrive in a natural manner at this, that chemio-therapeutic agents, built up in a complicated manner, may be compared to a poisoned arrow ; the fixing group of the drug which anchors itself to the chemo-receptor of the parasite corresponds to the point of the arrow, the binding member is the shaft, and the poison group is the arrow poison fixed to the shaft of the arrow. According to this scheme in the case of salvarsan (dioxydiamidoarsenobenzol) the benzol group would correspond to the shaft, the orthoamidophenol group to the point, and the trivalent arsenic group would correspond to the toxophoric group.

If we continue this comparison, then the substances which are used for poisoning the arrows are alkaloids and similar substances, which act injuriously on certain definite vital organs of the body ; and so we shall also have to assume that the toxophoric grouping of the synthetic drugs poisons the protoplasm of the bacterial cell, and this only appears to be possible when a chemical affinity exists between the toxophoric grouping and the constituents of the cell. The circumstance that all the derivatives of arsenic, which contain arsenic in the pentavalent form, i.e. in the fully saturated form, do not bring about any therapeutic action, but that this only commences when the arsenic group exists in the unsaturated condition corresponding to the trivalent radical, certainly points in the same direction. This difference between the saturated and unsaturated arsenic radical was discovered by the master mind of Bunsen, for in the year 1843, in his comparative studies relating to the non-poisonous cacodylic acid with the pentavalent arsenic and its poisonous reduction product the cacodyl with the trivalent arsenic, he came to the conclusion that ' the cacodylic acid had lost the power to form an attacking point, and at the same time it had lost its effect on the organism '. In the subsequent period

a very large series of analogous cases have become known corresponding to this truth, which point to the increased effectivity of the unsaturated radical. The best-known example is doubtless the high degree of toxic power of carbon monoxide as compared with the almost indifferent carbon dioxide.

Dyes act as bactericides only as such, but not in the form of their colourless products which correspond to the saturated type. *The fact is that all these unsaturated combinations contain unsatisfied avidities which render them capable of reacting additionally with other combinations.*

If, therefore, we poison a spirochæta with salvarsan, then there occur at least two different chemical fixations: first of all the fixation of the orthoamidophenol group, which primarily fixes the salvarsan to the parasite. It is only in consequence of this fixation that secondarily the trivalent arsenic group is given the opportunity of entering into chemical combination with the arseno-receptor of the cell, and so to exert its toxic effect. The avidity of the arseno-receptor can in itself be such that it can only react if favouring factors, which chemically must be regarded as a stereo-chemical facilitation, come into action.

Examples of such stereo-chemical facilitations are frequently found in chemistry, e.g. in the chemistry of the ortho-condensations. And so the haptophoric group of the arsenic molecule primarily brings the arsenic along to the cell and secondarily brings about its possibility of action.

Now, it is a frequent practice of many uncivilized peoples, in order to be certain of killing their enemies, that they not only rub over their arrow with one kind of poison but with two or three totally different kinds of poison. And so it also appeared advisable to imitate this procedure against the parasites, which is otherwise not very praiseworthy, and to poison our synthetically poisoned arrows not singly but doubly. In association with Dr. Karrer I succeeded in depositing the reduced arsenic compound, e.g. salvarsan, even on metals, and so in arriving at remedies which, used experimentally on animals, show an increased effect.

In the previous remarks I have described the conditions which are necessary in order that a certain substance may exert a parasiticidal effect, and indeed must effect such, if it operates directly on certain definite parasites in an aqueous solution, such as, for instance, is the case with the ordinary disinfectants. In the manner described above it is easily possible to arrive at a very large number of substances which will destroy bacteria and allied substances in aqueous solutions. But, of course, the problem is much more difficult when it is a question of internal disinfection or of the destruction of living parasites within the infected organism. If the problem is set before us of sterilizing a room, then indeed it is an easy matter to do so, owing to the present advancement of science; but the task becomes more difficult when the room is filled up with materials; and when these materials are of such a delicate sensitiveness as living cells, then the difficulty of the problem will be manifest without any further

explanation. As a matter of fact, it has proved that substances which bring about a colossal bactericidal effect in aqueous solutions even when they are highly diluted, are totally ineffective in therapeutics properly so called. For it has turned out that, generally speaking, these disinfectants are more or less powerful cell poisons, and seriously injure the organism; they are, therefore, not only parasitotropic but also *organotropic*.

Now, it depends exclusively on the relationship between parasitotropic and organotropic as to whether a certain disinfectant can be used as a remedy. In Robert Koch's celebrated experiment, in which even the largest doses of sublimate did not produce even a trace of therapeutic effect on anthrax infection, it is evident that the parasitotropic effect was reduced to nil by the organotropic effect. If the relationship of organotropic to parasitotropic is somewhat more favourable, then one may observe a peculiar phenomenon, consisting in the course of the infection being rendered worse to an extraordinary degree by the remedy, owing to the effect that the parasites increase to a much greater extent than is generally the case.

This phenomenon, discovered by Hata, is explained by the fact that the ratio of organotropic effect to parasitotropic effect is of such a nature, that almost the whole of the poison is absorbed by the organism, but only in infinitesimal quantities by the parasites. According to a biogenetic foundation principle it is quite a common thing for substances, which act destructively in *large* quantities, to bring about an *increase in the vital functions* in smaller doses. Only such substances, therefore, can be used as therapeutic agents in which the ratio between organotropic effect and parasitotropic effect is a favourable one, and that can be easily ascertained by experiment by a comparison between *dosis toxica* and *dosis tolerata*. *Only such substances can be considered therapeutic agents of which a fraction of the dosis tolerata is sufficient to bring about therapeutic effects.*

The organotropic effect of drugs is, of course, to be attributed, according to the views of Langley and myself, to this, that there are, in the most various cells of the body and its organs, quite different chemo-receptors, exactly in the same manner as we have postulated for the parasites. Apart from the pharmacological effect of the various remedies, this chemical difference of the organs appears clearly in the vital colouring.

I will mention here—in order only to indicate a few examples—the methyl blue colouring of the nerve trunks, the neutral red colouring of the cell granules, and the distribution of the isamin blue in the so-called pyrrol cells, so carefully and excellently investigated by Edwin Goldmann. The pathologico-anatomical findings point also to a chemical divergence on principle. When we see that after the introduction of paraphenylendiamine only the summit of the diaphragm assumes a black colouring; when we see that vinylamin in the case of all kinds of animals isolates and injures the renal papillæ and causes them to die; when after the introduction of cyanosin, as Hata and Goldmann have found, certain

definite regions in the hair of mice become coloured, and the colouring matter becomes stored to the greatest degree in the milk glands ; when a colouring material of the pyronin series in the case of mice brings about a general dropsy amounting to 50–60 per cent. of the body without injuring the kidney, which doubtless is only to be referred to an alteration of the vessels of the subcutaneous connective tissue ;—then all these phenomena can only be explained by the fact that at these particular spots definite chemical connexions of a specific nature must take place, which must be referred to the presence of certain definite chemo-receptors.

Now, according to the above representations, all these fixations are dependent on the haptophoric grouping of the drugs, and, therefore, it was a matter of great interest to observe how phenylarsenic acid, the mother-substance of the modern arsenic compounds, behaves when various different groups are attached thereto. In this connexion it has turned out that when we introduce different constituent fixation groups, e.g. chlorine, the oxygen group, the hydrocyanic acid group, the sulphuric acid group, the ammonia radical, we can manufacture, starting out from one substance, a series of combinations, the toxic effect of which may vary fifteen hundredfold. The combinations which are to the greatest extent free from poison—these are derivatives of sulphuric acid, especially the sulpho-phenylarsin acid and its salts—are less toxic than sodium chloride, and on the other hand there are substances the very smallest quantity of which bring about death. And in this connexion we can see that according to the nature of the substances, very different organs of the animal's body are injured. Sometimes it is the intestinal tract and the animals die of profuse diarrhœa ; sometimes it is the liver, and the mice—a rare occurrence—become jaundiced and die of serious alterations in the liver ; sometimes the red blood corpuscles become dissolved and the animals die of severe anæmia. Frequently also the central nervous system becomes injured, and in the case of mice this usually relates to the vestibular nerve of the inner ear. The interference with the equilibrium, produced in this way, causes the mice constantly to turn in circles just like the Japanese dancing mice. In the case of human beings the optic nerve is the point of attack for numerous derivatives of phenylarsin acid. The cases of blindness which have been observed after the use of very large doses of atoxyl, arsazetin, and other drugs are due to this injury.

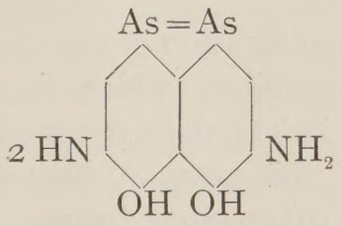
From this it is evident that according to the selection of the group annexed to the phenylarsin acid quite different organs will be affected. This is only explained according to the above views by the fact that there are, as already previously stated, in the various organs specific chemo-receptors which energetically attract certain fixation groups somewhat as the magnet attracts iron. And this view also provides us with the principle *according to which we have to construct our poisoned arrows.* We must attach to the phenylarsin acid group, or as the case may be to the

phenylarsenobenzol group, such grouping as is only related in a small degree to the organs of the sick body, but, on the other hand, is very closely allied to the receptors of the parasites.

I have explained above that the parasites possess a whole series of chemo-receptors which are specifically different from one another. Now if we can succeed in discovering among them a grouping which has no analogue in the organs of the body, then we should have the possibility of constructing an ideal remedy if we select a haptophoric group which is especially adjusted to the functions of the parasites.

A remedy provided with such a haptophoric group would be entirely innocuous in itself, as it is not fixed by the organs ; it would, however, strike the parasites with full intensity, and in this sense it would correspond to the immune productions, the anti-substances discovered by Behring, and which after the manner of the bewitched balls fly in search of the enemy. Let us hope that it will be possible chemio-therapeutically to hit the bull's eye in this manner also. I do not consider this at all out of the question, as it may be proved in certain sicknesses, e.g. spirillosis in hens, that from the fiftieth to the hundredth part of the *dosis tolerata* of salvarsan entirely frees the animals from the parasites and leads to a cure. Such a dose truly represents a nil dose, as the hen cannot be damaged thereby in the slightest degree. But such favourable conditions have only very rarely been discovered up to the present ; we shall have to be satisfied if we can succeed in obtaining good therapeutic results with the tenth or even the fifth or sixth portion of the *dosis tolerata*.

In the main the above are the principles which guided us in the construction of the new remedies. Among the numerous combinations which have been tested in experiments on animals in the case of trypanosomes and spirillar infection, and in the preparation of which I have been supported by the untiring co-operation of Dr. Benda, Dr. Bertheim, Dr. Kahn and Dr. Karrer, and which have been biologically tested, especially by my respected friend Professor Dr. Hata, and later by Dr. Castelli and Dr. Gonder and Frl. Leupold, salvarsan has proved to be the most efficient, the dioxydiamidoarsenobenzol of the formula




Here the orthoamidophenol group acts as the conducting and the arsenic group as the toxophoric group.

But now, gentlemen, the step from the laboratory to practice, i.e. to the bed-side, is an extraordinarily difficult and dangerous one—a step which can only be taken with the greatest care. Its difficulty and danger are in the main based upon two factors : (1) On the fact that in the case of men there exist so-called idiosyncrasies, forms of supersensitiveness which

do not occur in the case of animals. So, for instance, it is known that with a large number of thoroughly healthy persons, the use of harmless articles of food such as strawberries, crabs, &c., brings about unpleasant skin eruptions, and almost half the known remedies can incite such phenomena of supersensibility. It will not be a cause of surprise, therefore, that such phenomena may occur in a particularly serious form with the employment of therapeutic agencies which contain such powerful acting radicals as arsenic and mercury. I have already referred above to the disturbances of vision and cases of blindness which are produced by certain arsenic compounds.

Fortunately, it is proved that such primary supersensibility in the case of salvarsan is one of the very rarest phenomena, and that it was perhaps due to a number of other circumstances, sources of error of a hidden nature, which in many cases have led to the mistaken idea that supersensibility existed. In this place we must first of all mention Wechselmann, McIntosh and Fildes, Hort and Penfold, who have brought forward the very important proof that the destroyed bodies of bacteria which may occur in sterilized water are capable of bringing about a series of serious and unpleasant phenomena such as fever, vomiting, diarrhœa, &c. And even in the case of a pure unexceptionable water, technical mistakes in the manufacture of the salvarsan solutions may bring about injury ; too large an addition of alkali injures the veins used for the injection ; too small a degree of alkali brings about blood coagulation, and leads to thrombosis ; and a lengthy shaking of the solutions and standing in the air oxidizes the drug to a toxic product, the so-called oxide of arsenic, which is much more highly toxic than salvarsan.

(2) It has been shown that certain illnesses of a constitutional nature can cause a supersensibility. So, for instance, tuberculosis of the suprarenal region, the so-called Addison's disease, is an illness which, according to the observations of Wechselmann and myself, brings about a severe supersensitiveness of the patients to arsenic compounds, and the same applies also to the status lymphaticus, which, as has already long been known, must be regarded as a type of the constitutional lack of resistance and supersensitiveness.

Furthermore, the seat and location of the disease may also bring about supersensibility, a supersensibility which is excited by the so-called ' local reaction '. We are indebted to the master-mind of Robert Koch for the first knowledge of this peculiar phenomenon : the well-known tuberculin reaction of the tuberculous focus. Exactly similar reactions may, however, occur when, in a focus filled with parasites, the parasites are rapidly dissolved. Then under the influence of the liberated toxin an irritation of the tissues sets in which is connected with hyperæmia and swelling, and which is known in the case of the ' luetic ' illnesses as ' Jarisch-Herxheimer's reaction '. Such reactions are, of course, of no great importance in connexion with the skin tissues ; but if the reacting centres have their seat in the neighbourhood of vital organs (brain), then

the swelling may perhaps bring about injury of a nature serious to life, or even death itself. Indeed, it is well known that tuberculous meningitis may be influenced in an exceedingly dangerous manner by a careless tuberculin reaction ; in spite of this, however, no one will think of attributing the nervous disturbances to a neurotropia of tuberculin. And exactly the same phenomena may occur with salvarsan also if the spirochætæ of syphilis have localized themselves in the central nervous system.

As you will see, the treatment of patients is an exceedingly difficult and responsible task, and the clinical pioneers such as Schreiber, Wechselmann, Iversen, &c., deserve our warmest thanks. They have thrown the first light upon the most important questions (dosology, indications and counter-indications). From a series of observations, which is now so vast that it can hardly be surveyed, there has, however, resulted what I might call the 'therapeutic tactics', and which I should here like briefly to explain.

(1) The *Therapia sterilisans magna*, which consists in this, that by means of one or at most two injections the body is freed from the parasites. In experiments on animals, and also in the case of a series of important maladies, this principle can be carried through in a clear and pure manner. Here, therefore, the old therapeutic remedy is applicable : ' Frapper fort et frapper vite.' It is a matter of course that the necessary dose must be greater in proportion to the advance of the disease, for it is absolutely clear that if a definite number of parasites is destroyed by a certain definite dose of the remedy, the quantity must be multiplied if the number of parasites—as happens during the course of the infection—has likewise multiplied. Apart from this, by a rapid destruction of the parasites endotoxins are set at liberty which, with increasing numbers of parasites, reach the circulation of the blood in ever-increasing concentration. And then, frequently at the height of the disease, serious or irreparable pathological disturbances occur, such as suppuration or necrosis, which of course continue even when the pathogenic cause has been destroyed, and may lead to unpleasant complications.

I refer here to the typhoid ulcers and to the abscesses and necroses in the case of horse sickness.

Therefore, it is in my opinion necessary to ALLOW THE THERAPEUTIC TREATMENT TO COME INTO ACTION AS EARLY AS POSSIBLE, as under these circumstances the full success is most easily and most surely attainable. And it is just in these present times when, owing to the progress of diagnosis, and especially the modern assistance rendered by the microscope and serological investigations which are connected with the names of Widal, Rubner, and Wassermann, we are in a position to recognize the specific infections early, we must select as the first principle of medical treatment : ' Frapper vite.'

We shall now have to ask ourselves the question, what are the causes which make it possible for such a favourable result to be obtained, a result which may be taken as *Therapia magna sterilisans*, radical cure of the body by means of a single injection? Typical antibodies can be shown

to be produced fairly rapidly by the destruction of parasites and especially of protozoa. Hence, it is quite evident that this assisting action of the organism ought to be eminently efficacious. For if the medicine has destroyed not the whole of the parasites, but only 95 per cent., and 5 per cent. have resisted its action, then these remaining 5 per cent. are sure to succumb to the influence of the antibodies which are rapidly formed. If this is the case, the *Therapia sterilisans magna* is attained. Unfortunately, it has been shown that this salutary process may frequently be minimized considerably owing to the biological properties of the parasites. For it may happen that a part of the parasites which survive the first injection escape destruction by the serum either wholly or in part, and subsequently change into new varieties which have become serum proof, and which are known as a relapsing crop. The possibility of forming a relapsing crop largely depends on the nature of the parasites. In the case of spirillosis of fowls, which, as is known, is a disease taking a typical course, relapsing crops do not seem to form, and therefore the chemio-therapeutic cure is an eminently easy one. In cases of recurrent or relapsing fever in human beings, the number of the relapsing crops is restricted to three to four. The number of relapses which we have observed clinically corresponds exactly to the existence of the various relapsing strains. On the other hand, other parasites can exist in an extraordinarily great variety of relapsing strains, and in this connexion I need only mention the trypanosomes and, in particular, the parasite of human syphilis. In particular, in collaboration with Dr. Röhl and Frl. Gulbransen, and lately with Dr. Ritz, I have been able in the case of mice to produce, and to transmit for any length of time, eight entirely different forms of growths. It is clear that parasites of this kind which are able to form such a large number of relapsing crops offer very great difficulties in their treatment, as in this case the auxiliary forces of the body fail to act, so that it is necessary to do one's utmost to destroy the whole of the parasites all at once by means of drugs, as owing to their great power of adaptation a single germ surviving may perhaps be the cause of the infection breaking out afresh.

At this juncture the question arises as to what are the causes of some of the germs being able to escape disinfection.

If a certain exactly definable quantity of an antiseptic is added to a liquid containing bacteria (suspension of bacteria), a complete disinfection takes place; not a single germ escapes the destructive influence. However, such ideal conditions do not obtain in living organisms. Even in disinfecting a room we sometimes find that in certain places, in the so-called 'dead corners' formed by piping, water-pipes, &c., the gases of the disinfectant do not act sufficiently. In like manner the parasites which have settled in such 'dead corners' of the organism are not reached by the medicine.

Practical tests have, however, quickly taught us where such 'dead corners' are to be found in the organism; the principal one is the hollow

situated between the spinal cord and the dura, which is filled with a liquid as clear as water and almost entirely free from cells and albumen, the cerebro-spinal fluid. This condition of the cerebro-spinal fluid can only be accounted for by the fact that the cells by which it is secreted are in a high degree impervious to most of the constituents of the organism, for example, albumen, and that they only permit a limited quantity of substances with small molecules to pass through. The drugs with more complex molecules are thus kept back, like albumen, and cannot get into the cerebro-spinal fluid. Should, therefore, parasites be lodged in these places, it is impossible for the drug to attack them. This localization of the parasites is of very special importance in connexion with the para-syphilitic diseases, tabes and paralysis.

Another possible explanation of the deficient sterilization is this, that among the large number of parasites there may be some which are unaffected by certain drugs, thus resisting sterilization. On the whole I am of opinion that this fact does not play a very great part in the course of fresh infection, but that it becomes prominent in connexion with those frequently recurring diseases which are characterized by innumerable relapsing crops, such as sleeping sickness, lues, &c.

Here two possibilities are conceivable: Firstly, if sleeping sickness, for example, is treated with atoxyl in the usual manner it is possible—as can be demonstrated easily by experiment—for an atoxyl-proof stock to form itself by adaption.

But secondly, as I have already mentioned, the mere continual formation of relapsing crops, likewise in the course of time and of several generations, alone can bring about a change in the chemo-receptors of the parasites, which, according to circumstances, may result either in an increased or a reduced power of resistance of the parasites. For instance, I have found that a trypanosome strain, which was not affected by trypan red, lost this peculiarity after having passed into a relapsing crop.

We should, of course, expect that certain relapsing crops, especially those showing a great tendency to relapse, should become much less sensitive than the original stock. And the serious influence of the usual specifics, mercurial and arsenical, upon parasyphilitic diseases, in connexion with which Noguchi has lately proved the presence of living spirilla, tend to show that this is the case here.

These few facts and considerations suffice to indicate in which cases we may rely upon the result of the chemotherapeutic treatment being entirely successful, besides being quick, and in which cases such a result is to be obtained less easily and only by a circuitous road. The latter is especially the case with chronically recurring diseases accompanied by localizations not easily reached. If we compare the fight against parasitic diseases with a state of warfare, we find that, on the one hand, great battles are fought which may lead to victory in the course of one or a few days. In combating bacteria such a victory would compare with *Therapia magna sterilisata*. If, on the other hand, a fortress has to be taken, the

goal cannot be reached with one single stroke, but it may take months and even years.

May I be permitted at this juncture briefly to point out the aids which are employed in connexion with a bacteriological siege :

1. When parasites are lodged in a dead corner and are in consequence difficult to reach, it has frequently been found advisable to employ, instead of one single injection, a long series of injections extending over several weeks, the so-called serial treatment, in accordance with the rule : ' Gutta Cavat Lapidem ', and in this connexion I would specially point to the results which Leredde of Paris and Dreyfus of Frankfort have obtained by these means.

2. In this connexion it is desirable to employ a therapeutic agent of as small a molecular volume as possible, such as urotropin, which has been successfully employed by S. Flexner in cases of infant paralysis.

3. Moreover, various writers (Touton, Duhot, &c.) have suggested rendering the plexus epithelium more pervious to the therapeutic agent by means of certain chemicals, thus causing more of the therapeutic agent to get into the cerebro-spinal fluid. Unfortunately this method so far has not led to any tangible results.

4. The possibility of making direct injections into the cerebro-spinal canal, in order to let more of the therapeutic agent get directly to the parasites contained in the fluid, has also suggested itself. Thus Ayres Kopke of Lisbon has injected suitable disinfectants into the cerebro-spinal canal, while Swift and Moore of the Rockefeller Institute have quite recently adopted a novel and interesting method in the treatment of tabes, which promises to be very valuable. They treat the patient by first injecting salvarsan ; shortly afterwards they draw blood from him and inject considerable quantities of the serum obtained from this into the spinal canal. This method is not only novel but suitable in so far as it obviates all possible ill effects on the sensitive central nervous system by employing serum obtained from the patient himself, while at the same time it is possible to apply the curative in sufficient quantities. The results obtained in this connexion were entirely satisfactory.

It is fairly obvious that all these measures aim on the whole at rendering the places which are not easily accessible more accessible for the therapeutic agent than is the case under ordinary conditions. On the other hand, however, the greater power of resistance of certain parasites has to be taken into account, and this is a purely chemical question which can only be solved by chemical means. The road leading to its solution which promises the best results is that of combined therapy.

From what has been said it will be seen that combined therapy is best carried out with therapeutic agents which attack entirely different chemoreceptors in the parasites. For instance, it is useless to combine euchsin with its nearest relative, methyl violet ; and it is useless to combine therapeutically trypan blue and trypan red, for both attack the same spots in the parasites, but it is necessary to select from each group the

most effective substance and then to combine the most suitable representatives of the various types. It is clear that in this manner a simultaneous and varied attack is directed on the parasites, in accordance with the military maxim, 'march apart but fight combined'.

In this connexion the interesting fact has been brought out that, when such combinations are used *quoad* organism, summation of the toxic properties of the various substances need not occur, whilst, *quoad* parasite, the therapeutic properties can be increased. To quote a case in point, it has been found that a sulphite of *p*-oxyphenylarsenic acid, which is ten times as poisonous as salvarsan, when added to salvarsan up to a certain percentage, did not render the mixture more poisonous. But the healing properties of this mixture were three to four times greater than those of salvarsan in connexion with trypanosome infection in mice. Such phenomena are quite common in connexion with combined therapy. If one injects a substance, as for instance (a) parafuchsin and (b) salvarsan simultaneously, the colouring matter is stored up by other receptors, and finds its way into other organs than does the salvarsan, so that by this method an increase in the toxicity does not take place, provided the components have been properly selected. In this case $\frac{1}{2}$ plus $\frac{1}{2}$ is not equal to 1, *quoad* affection of the organs, but smaller than 1. On the other hand, both substances are concentrated in the parasites, and their effects can consequently be added or, in favourable cases, can be multiplied. We thus obtain the therapeutical inequality $\frac{1}{4}$ plus $\frac{1}{4}$ plus $\frac{1}{4}$ equal to 1.

I have maintained this point for quite a long time, and some very remarkable studies upon the same subject have recently appeared from Morgenroth's laboratory, in which stress is laid on the suitability of multiple, ternary, and quaternary combinations.

Moreover, according to more recent experiments it seems advisable, in all cases where anti-substances are produced, systematically to incorporate these same in the combination, because the anti-substances require a receptor apparatus entirely different in nature from the chemo-receptors. Thus the combination of pneumococcal serum with methylhydrocuprein, as tried by Morgenroth, has proved very efficient in connexion with tests on animals executed by Neufeld, while Dr. Bierbaum discovered simultaneously at my institute that exactly the same holds good in connexion with a combination of dysentery serum and salvarsan.

Thus the value of the combinations is clearly shown, as they make it possible, always assuming that suitable substances are used, to effect a cure with the smallest possible doses and in the least harmful manner, and to eliminate any danger resulting from a maximum dose of one of the ingredients. A further advantage of combined therapy is this, that under the influence of two different medicines, the danger of rendering the parasites immune to arsenic, which naturally would be a very great obstacle in connexion with further treatment, is apparently greatly minimized. Thus it has been shown that, in the course of a prolonged quinine treatment, it may happen—the cases are fortunately not very

frequent—that the malaria parasites become quinine proof, so that therapeutical doses of quinine are no longer able to remove the parasites. If, however, such a patient receives an injection of salvarsan, the malaria parasites are destroyed at once, for although they may be quinine proof, they are not arsenic proof. Should the dose of salvarsan have been too small to prevent a relapse, and provided further quinine is given to the patient on the parasites again appearing in the blood, a curative effect may be obtained by means of quinine. Consequently the combination of quinine and salvarsan has the effect of neutralizing or minimizing the quinine-proof qualities of the parasites.

For all these reasons I think that combined therapy will in the future conquer an ever-increasing field of action. Thus, for instance, Broden, in the Congo, succeeded in connexion with sleeping sickness in the human subject—it is true only in the early stage of this infection, which is so difficult to fight against—in obtaining good results by the combination of salvarsan and two basic colouring matters (trypallavin and tryparosan) by treatment lasting about a week.

It is precisely in the manifold character of the possibilities of combination that I see a special advantage, and peculiar possibilities of development. When once we are acquainted with the majority of the chemoreceptors of a particular kind of parasite, which will be a long piece of work, occupying many hands and heads, we shall have the most far-reaching possibilities of simultaneous attack by various agencies. And on this account combination therapeutics are also absolutely pluralistic in contrast to antitoxins, which may be said to act rather in one single direction.

And now, gentlemen, may I be permitted to refer to a few practical results. You are all aware that with a number of spirillar diseases the principle of *Therapia sterilisans magna* has proved most successful. You are aware that it is possible by one single injection of salvarsan to cure frambœsia (yaws), which is also caused by spirochætes, and is a scourge of the tropics, curing it completely except in rare cases where unimportant relapses occur ; this has been shown by the work of Strong, Koch, and Castellani. Thus, in Surinam, a hospital, in which over 300 patients with frambœsia were constantly under treatment, was closed and turned to other uses after the introduction of the salvarsan treatment, as one single injection sufficed to cure the disease, and the patients could all be discharged but two. It is to be hoped that in this way it will be possible to altogether extirpate frambœsia.

Exactly the same favourable results have been attained with recurring fever in the human subject, the fever immediately subsiding after the injection of salvarsan, and the patients being cured by one injection. The very rare cases of relapse occasionally occurring are also readily curable.

To continue dealing with salvarsan, in syphilis, which is so closely related to frambœsia, a fair percentage of cures has been obtained in the

very first stage of the disease by a single injection of a large dose, but of course the abortive cure by intensive treatment is far more certain.

With Vincent's angina and the diseases of the mucous membrane of the mouth, which are caused by spirochætes of the mouth, *Therapia sterilisans magna* is possible ; in fact in many cases a mere local application of salvarsan suffices. I may here further mention tertian malaria, in which form, but in this form alone, salvarsan has proved successful, and blastomycosis (Petersen) and the Aleppo boil. As regards diseases of animals, which can be cured by one single injection of salvarsan, I might specially mention breast diseases of horses, which is of such enormous importance to the military authorities, and lymphangitis epizootica, the African glanders in horses.

Most important are the recent observations of Rogers, who found emetin to be a specific against the very serious amœbic dysentery. And if here it is indeed advisable and necessary to repeat the injections, yet the triumph of therapeutics remains unassailed ; it is all one to the patient as to whether *Therapia sterilisans* or *Sterilisans fractionata* is employed, provided only he is relieved of his sufferings in a harmless manner.

Piroplasmosis also, which exerts a disastrous action, causing serious diseases in cattle and dogs, may according to the observations of Nuttall be favourably influenced by a pigment belonging to the class of trypan colouring matters, viz. by trypan blue, which was first composed by Mesnil. As I am informed the fight against this disease has been taken up in a general manner at Pretoria under the auspices of Theiler. The injections are there performed not by veterinary surgeons, but by the farmers themselves, and they are glad to save their valuable animals scot-free from this serious disease.

It is indeed easy to understand that the schizomycetes, which in themselves are so much hardier than the tender protozoa and spirochætes, will offer an increased resistance to the attack of drugs. Naturally here too there are fine differences, and it is perhaps no accident that the pneumococcus, the protoplasm of which is, of course, most sensitive, should in the course of treatment also have shown itself to be particularly sensitive. (I refer here to the fine researches of Morgenroth in the treatment of laboratory animals infected with the pneumococcus by means of derivatives of quinine, especially ethylhydrocuprin.) But in the case of hardier bacteria, too, such as the Bacillus typhosus, the possibility of sterilization is not beyond hope. The first successful experiments in this sphere were carried out by Conrad on rabbits and later confirmed and extended by Uhlenhuth and his fellow workers on this species of animal.

If I briefly allude to the very hopeful experiments of Gräfin Linden, who has endeavoured to influence tuberculous infections favourably by means of combinations of copper and lecithin, and if I add that salvarsan also has been shown to have a beneficial action upon the malignant anthrax-bacillus, and upon that of glanders and, possibly, upon that of erysipelas, both in animal experiments and occasionally too in human

cases, then all that we know about the chemio-therapeutics of the specific bacterial diseases has been told, so that it is just in this direction that there lies a wide field still to be worked. This field, important as it is, is still in the very first stages of experimentation.

And if after what has been said we cast a glance over the development of medicine and especially of the fight against infectious diseases, we must recognize that in the last fifty years the most important advances have been made in every direction, advances connected above all with the names of Pasteur, Robert Koch, and von Behring.

On the one hand we have the isolation of the pathogenic bacteria, which was made possible really by the Koch method of the solid culture medium and in which Robert Koch's pupils and fellow workers, Löffler, Gafftey, Pfeiffer, in the first order, participated ; the study of protozoa, which started from Laveran's discovery of the germ of malaria ; the discovery by Löffler and Frosch, Roux and Nocard, of the viruses which pass through filters ; and the recognition of insects as intermediate hosts and transmitters of infectious diseases, which is connected with the name of Theobald Smith and which has led to the most important consequences.

On the other hand we have the study of the immunity theory which was first inaugurated so brilliantly by Metchnikoff and which received a new impetus from the wonderful discovery of antitoxin by von Behring, through which a wide new field, that of the science of immunity and the investigation of serums, was opened up, on which Pfeiffer, Bordet, Widal, Wassermann and many others, including myself, have worked with successful result. Some of the most valuable fruits of these labours from a practical point of view have been the diagnosis of diseases first in the form of the Widal-Grüber reaction, and later the Wassermann syphilis-reaction, the importance of which for diagnosis and therapeutics cannot be estimated.

All these discoveries, especially in regard to the ways of spreading diseases on the part of the infecting agencies, have, in accordance with the principle that ' Prevention is better than cure ', been made good use of in the fight against epidemics and for prophylactic measures, and have brought about an improvement surpassing expectation. In the second place, the struggle with diseases which have already broken out has been able to derive advantages from these discoveries, the most wonderful example being the diphtheria serum.

Now that the liability to, and danger of, disease are to a great extent circumscribed, so far as epidemics and many other diseases are concerned, the efforts of chemio-therapeutics are directed as far as possible to fill up the gaps left in this ring, more especially to bring healing to diseases in which the natural powers of the organism are insufficient. And I believe that now when definite and sure foundations have been laid for the scientific principles and the method of chemio-therapeutics, the way is visible before us ; not always an easy but yet a practicable way. In the diseases involving protozoa and spirilla extraordinarily

favourable results, as I have shown, have already been gained, which can also satisfy far-reaching tests. There are many valuable indications that in a series of other diseases—small-pox, scarlatina, typhus exanthematicus, perhaps also yellow fever, and, above all, infectious diseases caused by invisible germs—the prospects of success are brightening. But in contra-distinction to these super-parasites the ordinary or common bacterial diseases (diseases due to the streptococcus and the staphylococcus, coli, typhoid and dysentery, but above all tuberculosis) will still require a hard struggle. Nevertheless, I look forward with full confidence to this development also, and might, without being set down as an optimist, put forward the view that in the next five years we shall have advances of the highest importance to record in this field of research. There are indeed problems which often prove too great for the powers of individuals, and can only be solved by a many-sided effort. Considering the enormous number of chemical combinations which are taken into consideration in a struggle with diseases, it will always be a caprice of chance or fortune or of intuition that decides which investigator gets into his hands the substances which turn out to be the very best materials for fighting the diseases, or the basal substances for the discovery of such. But the chances in favour of finding a real cure, and so of winning the big prize, will naturally rise with the number of those who occupy themselves with the definite problem. It is just at this point above all that necessity arises to gather and unite all powers, and here special force attaches to that motto ' Viribus unitis ', which gives guidance in so many other fields : which in so exemplary and fine a way is the foundation of this great International Congress, to which thousands have been drawn from all lands, to give their testimony that in the world of science all national barriers have disappeared.

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